

CITATION NO.: 8  
SERIAL NO.: 10/500,536  
INVENTOR: Brocchini & Godwin  
DOCKET NO.: POLYT9200WOUS



Europäisches Patentamt  
European Patent Office  
Office européen des brevets



Publication number: **0 496 472 A1**

## EUROPEAN PATENT APPLICATION

Application number: 92200160.7

Int. Cl.<sup>5</sup> **C08F 246/00, C08F 212/14,  
G01N 33/532**

Date of filing: 21.01.92

Priority: 25.01.91 US 646132

Date of publication of application:  
29.07.92 Bulletin 92/31

Designated Contracting States:  
**BE CH DE FR GB LI NL**

Applicant: **EASTMAN KODAK COMPANY**  
343 State Street  
Rochester, New York 14650-2201(US)

Inventor: **Sutton, Richard Calvin, c/o Eastman  
Kodak**  
Company Patent Department, 343 State  
Street  
Rochester, New York 14650-2201(US)  
Inventor: **Ponticello, Ignazio Salvatore, c/o  
Eastman Kodak**  
Company Patent Department, 343 State  
Street  
Rochester, New York 14650-2201(US)  
Inventor: **Danielson, Susan Jean, c/o Eastman  
Kodak**  
Company Patent Department, 343 State  
Street  
Rochester, New York 14650-2201(US)  
Inventor: **Oenick, Marsha Denise Bale, c/o  
Eastman Kodak**  
Company Patent Department, 343 State  
Street  
Rochester, New York 14650-2201(US)

Representative: **Nunney, Ronald Frederick  
Adolphe et al**  
Kodak Limited Patent Department Headstone  
Drive  
Harrow Middlesex HA1 4TY(GB)

**Succinimide containing polymers and latices prepared from same.**

Water-insoluble, noncrosslinking, nonporous copolymers are provided which have recurring units derived from:

- from 80 to 99.9 mole percent of one or more ethylenically unsaturated polymerizable oleophilic monomers which provide hydrophobicity to the copolymer, provided that none of the monomers are crosslinking monomers,
- from 0.1 to 20 mole percent of one or more ethylenically unsaturated polymerizable monomers having a succinimidoxycarbonyl group, and
- from 0 to 10 mole percent of one or more ionic or polar hydrophilic ethylenically unsaturated polymerizable monomers. These copolymers have a variety of uses, including diagnostic assays.

This invention relates to succinimidoxycarbonyl group-containing copolymers useful in diagnostic methods and analytical elements.

There is a continuing need in various research and industrial arts for polymerizable monomers which can be polymerized into useful copolymers.

Biologically active substances have been immobilized to advantage on particulate substrates such as polymeric particles. In some cases, the polymeric particulate substrates are fashioned or chemically treated to provide reactive groups on their outer surfaces for appropriate reaction with the biological substance. One means of producing such polymeric particulate substrate is to prepare the polymers with monomers having the appropriate reactive groups.

US-A-5,030,697 relates to a polymer-bound linkable dye having a water-soluble copolymer, a dye covalently bound thereto, and functional groups enabling the polymer dye to link covalently with biological materials.

Undesired non-specific protein adsorption has been a continual problem encountered when using polymeric material as the solid substrate in analytical and diagnostic methods. Non-specific protein adsorption is of concern in affinity chromatography as well as in assays, where non-specific adsorption causes unwanted background and obscures true results.

The hydrophilic nature of the polymer surface has also been the subject of considerable research because an increase in hydrophilicity reduces adsorption of some protein but not others.

There is a need in the industry for material from which solid substrates may be made wherein the material is water-insoluble, non-porous, and capable of attachment to chemical and biological materials.

The needs in the art noted above are met with a water-insoluble, noncrosslinking, nonporous copolymer.

the copolymer characterized wherein the recurring units are derived:

(a) from 80 to 99.9 mole percent of one or more ethylenically unsaturated polymerizable oleophilic monomers which provide hydrophobicity to the copolymer, provided that none of the monomers are crosslinking monomers.

(b) from 0.1 to 20 mole percent of one or more ethylenically unsaturated polymerizable monomers having a succinimidoxycarbonyl group, and

(c) from 0 to 10 mole percent of one or more other noncrosslinking ethylenically unsaturated polymerizable monomers.

This invention also provides a novel aqueous latex composition comprising nonporous particles wherein at least the outer surface is composed of water-insoluble, noncrosslinked copolymer,

the composition characterized wherein the copolymer has recurring units as described above.

The advantages of the copolymers of this invention are that they contain a functional comonomer which survives the polymerization process. The comonomer is capable of subsequently reacting with nucleophiles such as proteins, nucleic acids, peptides and amino acids and other amino or sulfhydryl containing materials. Also, the latex particles can be directly made without hydrolysis of the succinimidoxycarbonyl active ester group.

Further, the copolymers of the invention are hydrophobic to such a degree that they approach and are more readily absorbed to the surface of the protein in comparison to the ability of known copolymers to receive protein.

The copolymers are also useful in the composition of this invention which provides particles which are colloidally stable to the biological chemistries of immobilization and detection, even when coated in a web format. These particles have the additional advantages of being free of surfactants and protective colloids, nonporous, and monodisperse.

Copolymers of this invention can also be used in forming particles used to produce gel-grafted matte bead layers in photographic elements. Other photographic uses of such polymers, such as polymeric gelatin hardeners, hardenable binders or vehicles, and thickeners would also be readily apparent to a skilled worker in the art.

Preferably, the polymers of this invention are used to provide reagents for medical, analytical or diagnostic methods. The structural advantages of the succinimidoxycarbonyl group in the essential monomers used herein are its reactivity with styrene monomers, its hydrophobicity and its resistance to hydrolysis.

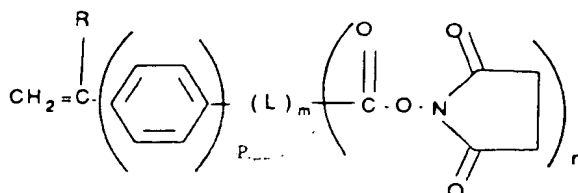
More particularly, the copolymers of this invention have recurring units derived:

(a) from 80 to 99.9 mole percent, more preferably from 90.0 to 99.9 mole percent, of one or more ethylenically unsaturated polymerizable oleophilic monomers which provide hydrophobicity to the copolymer, provided that none of the monomers is crosslinkable,

(b) from 0.1 to 20 mole percent, more preferably from 0.1 to 10 mole percent of one or more

ethylenically unsaturated polymerizable monomers having a succinimidoxycarbonyl group, and (c) from 0 to 10 mole percent, and more preferably from 0 to 3 mole percent of one or more other non-crosslinking ethylenically unsaturated polymerizable monomers such as ionic or polar hydrophilic monomers.

Preferably, the copolymer comprises recurring units derived from monomer (b), as described above, which can be represented by the structure:



wherein:

R is hydrogen, alkyl of 1 to 3 carbon atoms or halo.

L is a linking group having at least 2 carbon atoms in the linking chain consisting essentially of a combination of at least two of alkylene groups having 1 to 8 carbon atoms, arylene groups having 6 to 12 carbon atoms, hetero atoms or heteroatom-containing groups.

m is 0 or 1, n is 1 or 2, and P is 0 or 1, with the proviso that when n is 2, one of the alkylene and arylene groups is necessarily trivalent.

More specifically, in the structure noted above, R is hydrogen, alkyl of 1 to 3 carbon atoms (such as methyl, ethyl, isopropyl and n-propyl), or halo (such as chloro or bromo). Preferably, R is hydrogen, methyl or chloro. More preferably, R is hydrogen or methyl.

Also, L is an organic linking group having at least 2 carbon atoms in the linking chain and is a combination of at least two of (1) alkylene groups having 1 to 8 carbon atoms, such as methylene, ethylene or trimethylene, propylene, tetramethylene, pentamethylene, or 2,2-dimethyl-1,3-propylene, (2) arylene groups having 6 to 12 carbon atoms, such as phenylene, tolylene, xylylene, naphthylene, and (3) divalent hetero atoms, such as oxygen (oxy), and sulfur (thio) atoms, or heteroatom-containing groups, such as carbonyl, sulfonyl, imino, ureylene, (-N'R where R is hydrogen or lower alkyl of 1 to 6 carbon atoms, such as methyl, ethyl, propyl, butyl, pentyl and hexyl).

The alkylene groups can have from 1 to 8 carbon atoms, and can be branched, linear or cyclical, substituted or unsubstituted with one or more alkyl groups (preferably from 1 to 8 carbon atoms, such as methyl, ethyl, isopropyl, hexyl and octyl), alkoxy (preferably from 1 to 12 carbon atoms, such as methoxy, ethoxy, propoxy, t-butoxy and octyloxy), cycloalkyl (preferably from 4 to 6 carbon atoms, such as cyclobutyl, cyclohexyl and cyclopentyl), aryl (preferably from 6 to 12 carbon atoms, such as phenyl, tolyl, xylyl, naphthyl, 4-methoxyphenyl and chlorophenyl). Such groups are not difficult to design or synthesize for one skilled in synthetic chemistry. The arylene groups can have from 6 to 12 carbon atoms in the aromatic nucleus, and can have the same substituents as described above for the alkylene groups.

Preferably, L comprises alkyleneoxycarbonylalkylene, alkyleneethioalkyleneoxycarbonylalkylene, alkyleneiminocarbonylalkylene, iminoalkyleneoxycarbonylalkylene, alkyleneethioalkylene, alkyleneethioalkyleneiminocarbonylalkyleneoxyalkylene, alkyleneethioalkyleneiminocarbonylalkyleneethioalkylene, alkyleneethioalkyleneiminocarbonylalkylene, alkyleneethioarylene, alkyleneethioalkyleneoxyalkyleneethioalkyleneoxycarbonylalkylene, alkyleneoxyarylenealkyleneethioalkylene, alkyleneethioalkyleneoxyalkyleneethioalkyleneoxycarbonylalkylene, alkyleneoxyarylenealkyleneethioarylenealkyleneethioalkylene, alkyleneethioalkyleneoxyalkyleneethioalkyleneoxycarbonylarylene, carbonyloxyalkyleneoxycarbonylalkylene, carbonyloxyalkyleneureylenealkylene, carbonyloxyalkyleneiminocarbonylalkylene and carbonyloxyalkyleneoxycarbonylalkylene.

Preferably, P is 1 and L is alkyleneethioalkylene, ethylenethiophenylene, or alkyleneethiophenylidyne.

Representative L groups include: methyleneoxycarbonyltrimethylene, methylenethioethyleneoxycarbonyltrimethylene, methyleneiminocarbonyltrimethylene, methylene-N-methyliminoethyleneoxycarbonyltrimethylene, methylenethioethylene, methylenethioethyleneiminocarbonylmethyleneoxymethylene, methylenethio-1,1,2-ethylidynemethylenethioethyleneiminocarbonylmethylenethiomethylene, methylenethioethyleneiminocarbonylmethylene, methylenethio-1-carboxyethylene, methylenethiophenylene, methylenethioethyleneox-

yethylenethiomethyleneoxycarbonylethylene, methyleneoxyphenylenemethylenethioethylene, methylenethioethyleneoxyethylenethioethyleneoxycarbonylethylene, methyleneoxyphenylenemethylenethiophenylenemethylenethiotrimethylene and methylenethioethyleneoxyethylenethioethyleneoxycarbonylphenylene.

Also,  $m$  is 0 or 1,  $n$  is 1 or 2, and  $P$  is 0 or 1, with the proviso that when  $n$  is 2, one of said alkylene and arylene is necessarily trivalent.

Most preferably,  $P$  and  $m$  are both 0.

Preferably, monomer (b) is styrene or a styrene derivative, or an acrylic or methacrylic acid ester. More preferably, N-acryloyloxysuccinimide, 4-(2-succinimidoxycarbonylethylthiomethyl)styrene, 4-[1,2-bis(succinimidoxycarbonyl)ethylthiomethyl]styrene, or 4-(2-succinimidoxycarbonylphenylthiomethyl)styrene.

While the monomers (b) described above can be polymerized to form homopolymers, preferably they are used to prepare copolymers with one or more additional ethylenically unsaturated polymerizable monomers. For instance, the oleophilic monomers identified above as (a) are useful for providing hydrophobicity or water-insoluble properties to the resulting copolymer. A mixture of such monomers can be used if desired. Such monomers would include, but not be limited to, vinyl aromatics (for example, styrene and styrene derivatives such as 4-vinyltoluene,  $\alpha$ -methylstyrene, 2,5-dimethylstyrene, 4-*t*-butylstyrene and 2-chlorostyrene), acrylic and methacrylic acid esters and amides (for example, methyl acrylate, methyl methacrylate, *n*-butyl acrylate, 2-ethylhexyl methacrylate, benzyl acrylate and *N*-phenylacrylamide), butadiene, acrylonitrile, vinyl acetate, vinylbenzyl acetate, vinyl bromide, and vinylidene chloride.

In addition, ethylenically unsaturated polymerizable monomers (c) other than those described above for monomers (a) or (b) can be copolymerized to provide desirable properties. For example, such monomers include anionic monomers containing sulfonic acid groups or salts thereof, including 2-acrylamido-2-methylpropane sulfonic acid, 3-methacryloyloxypropane-1-sulfonic acid, *p*-styrene sulfonic acid and salts thereof. Also included in the (c) group of monomers are nonionic hydrophilic monomers such as acrylamide, methacrylamide, *N*-isopropylacrylamide, 2-hydroxyethyl acrylate, 2-hydroxyethyl methacrylate, pentaerythritol monomethacrylate, *N*-vinyl-2-pyrrolidone and so on. In addition, monomers having active methylene groups, such as 2-acetoacetoxyethyl methacrylate, could be used.

The method of preparing the novel copolymers described above may be accomplished using standard emulsion or suspension polymerization techniques. Pore-producing substances or inert diluents are not used. If porosity is required and pore integrity needs to be maintained, the particles typically should be crosslinked so that the particles will not dissolve in the polymerization solvent or the inert diluent or pore-producing substances.

Typically, the particles of this invention are non-porous and do not require a crosslinked structure to be useful.

Suspension polymerization procedures are well known and generally involve mechanically dispersing the monomers in a liquid, usually water, and polymerizing the monomer droplets formed from the dispersing action. Polymerization initiators which are soluble in the monomer are generally used, and surfactants can also be used. Small particles of polymer are obtained with careful control of the polymerization conditions, which particles can be isolated using filtration, centrifugation or spray drying.

The copolymers of this invention are preferably prepared using emulsion polymerization techniques. In emulsion polymerization (whether batch, continuous or semi-continuous modes as known in the art), it is preferred that the copolymers be prepared as small particles without the use of surfactants (also known as emulsifiers). Further, the use of protective colloidal dispersing agents is not preferred. Residual surfactant or dispersing agents on the particles tend to interfere with attachment of biologically active substances (for example, antibodies and enzymes). Thus, the resulting latex is substantially free of surfactants and colloidal dispersing agents. Conditions for surfactant-free polymerization are known in the art. Continuous polymerization is the most preferred technique so that monomers are added to a reaction vessel over a period of time.

Some general conditions for emulsion polymerization include reaction of the monomers in the presence of water-soluble, free radical polymerization initiators (such as redox combinations of persulfates and bisulfites including potassium persulfate, ammonium persulfate, potassium bisulfite and sodium bisulfite and others known in the art) in an amount of from 0.1 to 5 weight % over a period of from 30 to 1200 minutes at a temperature of from 30 to 95°C. Other conditions include the use of chain transfer agents such as dodecanethiol at concentrations of from 0.05 to 5% (based on monomer weight).

A representative preparation of copolymers useful in this invention is provided in Example 1 below. Representative preparations of monomers useful in this invention are provided in Examples 2-4 below.

Certain preferred copolymers of this invention are generally provided in small particulate form (latices, predominantly spherical) having an average diameter of from 0.01 to 20  $\mu$ m. Preferably, the particles have

an average diameter of from 0.01 to 10 mm, and more preferably from 0.1 to 0.05 mm. The water-insoluble particles are generally nonporous and nonswellable in water or water-miscible solvents (such as alcohols), but they are also generally water-dispersible due to their small size. Polymerization procedures generally provide from 0.5 to 50 percent solids of copolymer, although, the latex composition of this invention generally has from 0.5 to 25 (preferably from 1 to 20) percent solids of copolymer particles when used.

Representative copolymers of this invention include, but are not limited to: poly[styrene-co-4-(2-succinimidoxycarbonyl)ethylthiomethyl]styrene] (mole ratio 96.5:3.5), poly[styrene-co-4-[1.2-bis-(succinimidoxycarbonyl)ethylthiomethyl]styrene] (mole ratio 97.5:2.5).

While in most cases, the polymers of this invention are homogeneous particles, it is essential that at least the outer surface of polymeric particles be composed of a polymer of this invention. Particles having an outer shell of the polymer can be prepared by graft copolymerization or other known procedures so that an already formed particle is coated with another polymer.

All percentages in the following nonlimiting examples are by weight unless otherwise indicated.

#### EXAMPLE 1

Preparation of poly(styrene-co-N-acryloyloxy-succinimide) (96.83/3.17 molar ratio or 95/5 weight ratio).

A suitable three-neck flask (1275 mL) completely filled with distilled water was used as the reaction vessel. At 80 °C, three chemical streams were simultaneously pumped into the flask. These three chemical streams comprised the following materials:

Stream 1 (monomer mix)-styrene, 765.70 g, N- acryloyloxysuccinimide, 40.73 g, dodecylmercaptan or 1-dodocanethiol, 8.06 g.

Stream 2 (oxidant)-water, distilled, 1349.91 mL,  $(\text{NH}_4)_2\text{S}_2\text{O}_8$ , 16.13 g.

Stream 3 (reductant)-water, distilled, 1349.91 mL,  $\text{Na}_2\text{S}_2\text{O}_5$ , 8.06 g. The pump rates were:

Stream #	Rate, g/min	Rate, mL/min
1	2.48	2.73
2	4.14	4.14
3	3.99	3.99

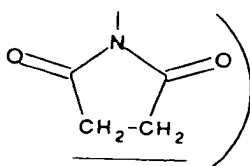
The theoretical solids based on flow are 23%, and the actual residence time was 128 minutes. After an addition time of 300 minutes, the reaction was stopped yielding 1081 grams of 21.4% solids. The resulting polymer latex was dialyzed for 5 days to yield 1366 g of purified latex of 16.2%. The NMR analysis of the polymer indicated a 97:3 mole ratio of styrene/succinimide monomers incorporated in the copolymer. Elemental analysis gave carbon of 89.78% (90.15% theory) and hydrogen 7.38% (7.50% theory). The particle size was 1.0 mm with a standard deviation of 0.05.

#### EXAMPLE 2

Preparation of 4-(2-succinimidoxycarbonyl)ethylthiomethyl]styrene

To a stirred solution of N-hydroxysuccinimide (7.0 g, 0.06 mole), and 3-(p-vinylbenzylthio)propionic acid (13.3 g, 0.06 mole) in chloroform (100 mL) was added N,N'-dicyclohexylcarbodiimide (12.6 g, 0.06 moles) in chloroform (50 mL) at room temperature. The mixture was stirred at room temperature and the temperature of the reaction increased to 37 °C. Within 5 minutes, the by-product N,N'-dicyclohexylurea began to precipitate. The reaction was stirred at 45 °C in a hot water bath for 1 hour and stirring was continued at ambient temperature overnight. The precipitated N,N'-dicyclohexylurea was then removed by filtration and the solvent was evaporated in vacuo. To the residue was added diethyl ether (100 mL) and the mixture was kept at -16 °C overnight. The white solid was collected by filtration, m.p. 63-68 °C, yield 93%.

Analysis Calculated for  $\text{C}_{15}\text{H}_{17}\text{NO}_4\text{S}$ : C, 60.17, H, 5.37, N, 4.39, S, 10.04. FOUND: C, 59.32, H, 5.35, N, 4.77, S, 9.23.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) w 2.8 (broad singlet, 8H,  $\text{CH}_2\text{CH}_2$ ).



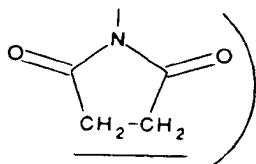
3.7 (s, 2H,  $\text{ArCH}_2$  S), 5.15 and 5.7 (AB quartet, 2H,  $\text{CH}_2$  =), 6.7 (m, 1H,  $\text{CH}$  =), 7.3 (m, 4H, Ar H's).

### EXAMPLE 3

#### Preparation of 4-[1.2-Bis(succinimidoxycarbonyl)ethyl-thiomethyl]styrene

This compound was prepared by the same procedure described above to give a white solid, which was recrystallized from dichloromethane-ethylacetate (4:1), m.p. 118-120 °C with polymerization, yield 83%.

Analysis Calculated for  $\text{C}_{22}\text{H}_{20}\text{N}_2\text{O}_5\text{S}$ : C, 54.78, H, 4.38, N, 6.08, S, 6.96. FOUND: C, 54.63, H, 4.41, N, 6.11, S, 7.36.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) w 2.8 + 2.85 (2 singlets, 8H,



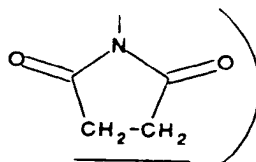
3.2 (m, 2H,  $\text{CH}_2\text{-CO}_2\text{NHS}$ ), 3.95 (t, 1H, S- $\text{CH}_2\text{-C}$ ), 4.05 (s, 2H,  $\text{CH}_2\text{-S}$ ), 5.2 and 5.75 (AB quartet, 2H,  $\text{CH}_2$  =), 6.7 (m, 1H,  $\text{CH}$  =), 7.38 (m, 4H, ArH's).

### EXAMPLE 4

#### Preparation of 4-(2-succinimidoxycarbonylphenylthio-methyl)styrene

This compound was prepared by the same procedure described above to give a white solid which was crystallized from dichloromethane (100 ml)/ethyl acetate (80 ml), m.p. 155-7 °C, yield 80%.

Analysis Calculated for  $\text{C}_{20}\text{H}_{17}\text{NO}_3\text{S}$ : C, 65.38, H, 4.66, N, 3.81, S, 8.73. FOUND: C, 64.91, H, 4.97, N, 3.97, S, 7.87.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) w 2.8 (s, 4H,



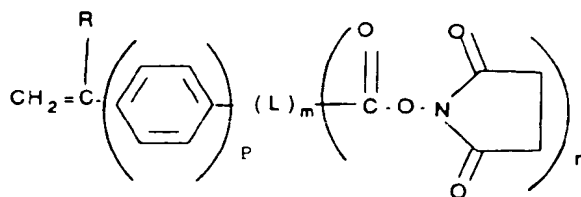
4.2 (s, 2H,  $\text{CH}_2\text{-S}$ ), 5.2 and 5.7 (AB quartet, 2H,  $\text{CH}_2$  =), 6.65(m, 1H,  $\text{CH}$  =), 7.0-8.2 (m, 8H, ArH's).

### Claims

1. A water-insoluble, noncrosslinked, nonporous copolymer, the copolymer characterized wherein the recurring units are derived:
  - (a) from 80 to 99.9 mole percent of one or more ethylenically unsaturated polymerizable oleophilic monomers which provide hydrophobicity to the copolymer, provided that none of the monomers are crosslinking monomers,
  - (b) from 0.1 to 20 mole percent of one or more ethylenically unsaturated polymerizable monomers having a succinimidoxycarbonyl group, and
  - (c) from 0 to 10 mole percent of one or more other ethylenically unsaturated polymerizable

monomers.

2. The copolymer as claimed in claim 1 having from 0 to 3 mole percent of recurring units derived from monomer (c).
3. The copolymer as claimed in either of claims 1 or 2 having from 0.1 to 10 mole percent of recurring units derived from (b).
4. The copolymer as claimed in any of claims 1 through 3 wherein monomer (b) is represented by the structure:



wherein:

$\text{R}$  is hydrogen, alkyl of 1 to 3 carbon atoms or halo.

$\text{L}$  is a linking group having at least 2 carbon atoms in the linking chain and is a combination of at least two of (1) alkylene groups having 1 to 8 carbon atoms, (2) arylene groups having 6 to 12 carbon atoms, and (3) hetero atoms or heteroatom-containing groups.

$\text{m}$  is 0 or 1,  $\text{n}$  is 1 or 2, and  $\text{P}$  is 0 or 1.

with the proviso that when  $\text{n}$  is 2, one of said alkylene and arylene is necessarily trivalent.

5. The copolymer as claimed in claim 4 wherein  $\text{R}$  is hydrogen, methyl, or chloro.
6. The copolymer as claimed in claim 4 wherein monomer (b) is N-acryloyloxy-succinimide, 4-(2-succinimidoxycarbonyl)ethyl-thiomethylstyrene, 4-[1,2-bis(succinimidoxy-carbonyl)ethylthiomethyl]-styrene, or 4-(2-succinimidoxycarbonyl)phenylthiomethylstyrene.
7. An aqueous latex composition comprising nonporous particles wherein at least the outer surface is composed of a water-insoluble, noncrosslinked copolymer, the composition characterized wherein the copolymer is that claimed in any of claims 1 through 6.
8. The composition as claimed in claim 7 wherein the composition is substantially free of surfactants and protective colloidal dispersing agents.
9. The composition as claimed in either of claims 7 or 8 wherein the particles have an average diameter of from 0.01 to 10  $\mu\text{m}$ .
10. The composition as claimed in any of claims 7 through 9 wherein the composition has from 0.5 to 25 percent solids of the copolymer particles.



European Patent  
Office

# EUROPEAN SEARCH REPORT

Application Number

EP 92 20 0160

## DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
A	EP-A-0 331 633 (CIBA-GEIGY AG) ---		C08F246/00 C08F212/14 G01N33/532
A	CH-A-601 364 (CIBA-GEIGY AG) -----		

### TECHNICAL FIELDS SEARCHED (Int. Cl.5)

C08F

The present search report has been drawn up for all claims

Place of search  
THE HAGUE

Date of completion of the search  
13 MAY 1992

Examiner  
CALWENBERG C. L.

### CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone  
Y : particularly relevant if combined with another document of the same category  
A : technological background  
O : non-written disclosure  
P : intermediate document

T : theory or principle underlying the invention  
E : earlier patent document, but published on, or after the filing date  
D : document cited in the application  
L : document cited for other reasons

& : member of the same patent family, corresponding document

ZPO FORM 1503 01.82 (P0601)



# Facile synthesis of well-defined water-soluble polymers *via* atom transfer radical polymerization in aqueous media at ambient temperature

X.-S. Wang, S. F. Lascelles, R. A. Jackson and S. P. Armes\*

School of Chemistry, Physics and Environmental Science, University of Sussex, Falmer, Brighton, UK BN1 9QJ.

E-mail: s.p.armes@sussex.ac.uk

Received (in Oxford, UK) 14th June 1999, Accepted 5th August 1999

CITATION NO.: 9

SERIAL NO.: 10/500,536

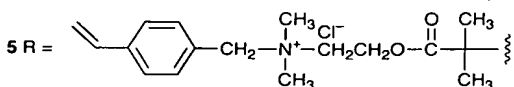
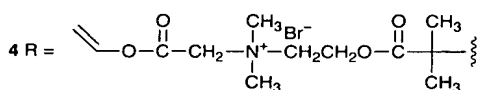
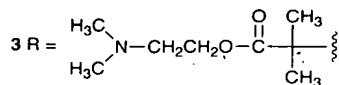
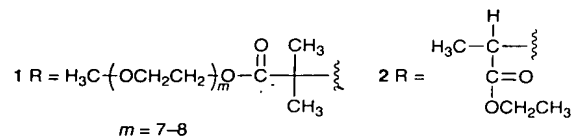
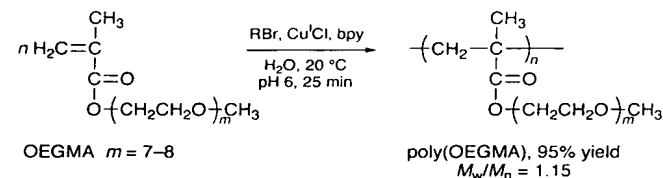
INVENTOR: Brocchini & Godwin

DOCKET NO.: POLYT9200WOUS

Monomethoxy-capped oligo(ethylene oxide) methacrylate (OEGMA) is readily polymerised in aqueous media by atom transfer radical polymerisation at 20 °C using various initiators; the resulting OEGMA polymers and macromonomers were obtained in high yield (> 95%) within short reaction times and polydispersities were as low as 1.12.

Atom transfer radical polymerisation (ATRP) which is applicable to both styrenic and (meth)acrylate monomers and is remarkably tolerant of functional groups.<sup>1,2</sup> With regard to hydrophilic monomers, recent ATRP publications describe: (i) the polymerisation of 2-hydroxyethyl acrylate in aqueous media at 90 °C;<sup>3</sup> (ii) the (co)polymerisation of 2-(dimethylamino)ethyl methacrylate either in bulk or in non-aqueous media<sup>4</sup> and (iii) the polymerisation of sodium methacrylate at 90 °C.<sup>5</sup> In this latter example polymerisation was slow and incomplete; yields of only 70–80% were obtained after 21 h. Herein we describe the efficient, well-controlled polymerisation of monomethoxy-capped oligo(ethylene oxide) methacrylate (OEGMA) *via* ATRP in aqueous media at 20 °C. Excellent yields (> 95%) are obtained in short reaction times (< 0.5 h) even at 20 °C. Moreover, vinyl functional initiators can be used to prepare well-defined OEGMA macromonomers.

Our ATRP formulation was based on that described by Matyjaszewski's group.<sup>1</sup> The transition metal catalyst was Cu<sup>I</sup>Cl and the ligand was 2,2'-bipyridine (bpy). Initiator **1** was synthesised according to a literature procedure.<sup>5,6</sup> A typical ATRP synthesis was carried out as follows (Scheme 1). Initiator



Scheme 1

**1** (232 mg, 0.54 mmol, 1 equiv.) was dissolved in 5 ml of doubly distilled de-ionised water. To this degassed solution was added the bpy ligand (211 mg, 1.08 mmol, 2 equiv.), followed by Cu<sup>I</sup>Cl (53 mg, 0.54 mmol, 1 equiv.). OEGMA monomer (9.70 g, 23 mmol, 42 equiv.) was added to this reaction mixture using a double-tipped needle and the solution was de-gassed using a nitrogen stream for 10–30 min with continuous stirring at 20 °C. The reaction solution became dark brown and much more viscous, indicating the onset of polymerisation; exotherms of 5–10 °C were typically observed. After 0.5 h, THF (50 ml) was added to the reaction solution, followed by excess MgSO<sub>4</sub> (15 g) to absorb the water. After filtration, the THF solution of poly(OEGMA) was passed through an alumina column to remove residual catalyst. THF was then removed under vacuum, yielding off-white polymers.

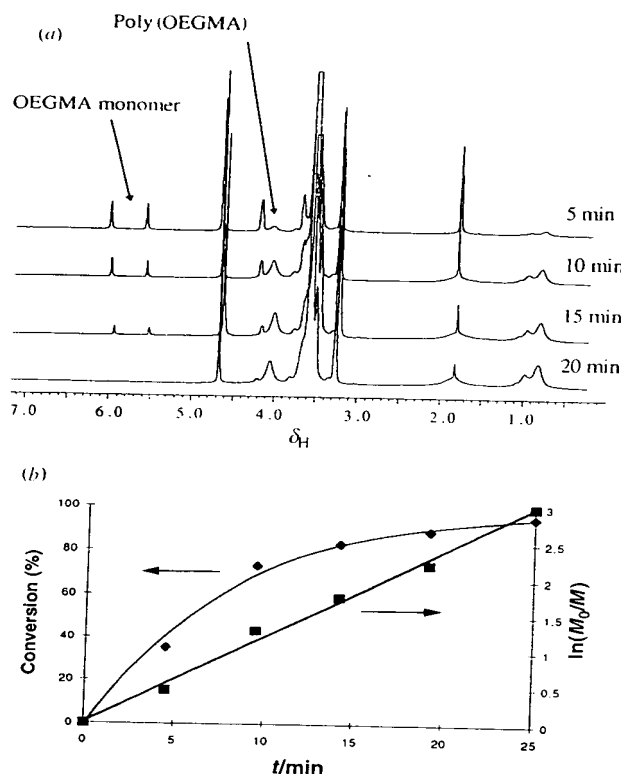
Molecular weight distributions were assessed using GPC (THF eluent; PMMA standards; RI detector). Polymer molecular weights, polydispersities and yields are summarised in Table 1. Conversion of OEGMA to polymer was monitored by <sup>1</sup>H NMR spectroscopy: Fig. 1(a) illustrates the progressive reduction of monomer vinyl signals at δ 5.4–5.8, accompanied by a concomitant increase in poly(OEGMA) signals (e.g. at δ 3.8–4.0). Fig. 1(b) shows a typical conversion *vs.* time curve derived from the NMR spectra. High conversions of monomer to polymer were obtained in short reaction times and the consumption of monomer followed first order kinetics, as expected. Narrow polydispersities ( $M_w/M_n < 1.12-1.30$ ), indicative of a living polymerisation, were obtained for initiators **1**, **2** and **4**. At present we have no explanation for the somewhat higher polydispersities obtained with initiator **3**.

Overlapping peaks prevented discrimination between the NMR signals due to the oligo(ethylene oxide) initiator **1** and the OEGMA residues. However, inspection of the <sup>1</sup>H NMR spectra (CDCl<sub>3</sub> or D<sub>2</sub>O) of the cleaned-up polymers prepared using initiators **2** and **4** confirmed the presence of the initiator, as expected. The peak integral of the NMR signal assigned to the α-proton of **2** at δ 2.1–2.2 (or to the azamethylene protons of **4** at δ 4.6) was compared to that due to the ethylene oxide protons of the OEGMA residues at δ 3.8–4.0 in order to determine the degree of polymerisation of the OEGMA chains by end-group analysis. Such calculations yielded number-average molecular weights ( $M_n$ ) which were in excellent agreement with those expected from the corresponding monomer/initiator ratios (see Table 1). Moreover, in the case of initiator **4**, well-defined vinyl acetate-capped macromonomers were obtained, which are expected to be useful reactive stabilisers for poly(vinyl acetate) latex syntheses. Facile synthetic routes to such well-defined hydrophilic macromonomers are very rare in the literature, although similar selectivity has been reported by Matyjaszewski's group for the preparation of hydrophobic polystyrene-based macromonomers by ATRP utilizing a vinyl chloroacetate initiator.<sup>7</sup> Our attempts to prepare the analogous styrene-capped macromonomers using initiator **5** under the same conditions were not successful. High molecular weights and broad polydispersities were obtained (see Table 1), which suggests insufficient selectivity: the styrenic end-groups probably copolymerise with the OEGMA even at 20 °C.

**Table 1** A summary of the molecular weights and polydispersities of various OEGMA-based polymers synthesised using ATRP in aqueous media at 20 °C. Synthesis conditions: [initiator] = 0.54–2.14 mmol; initiator:Cu<sup>I</sup>Cl:bpy was 1:1:2 in all experiments

Initiator	t/h	Conversion (%)	$M_n$			
			Target	<sup>1</sup> H NMR	GPC	$M_w/M_n$
1	0.5	> 99 <sup>a</sup>	8 500	—	6 500 <sup>b</sup>	1.12
1	0.5	> 99 <sup>a</sup>	16 300	—	9 700 <sup>b</sup>	1.17
2	2.0	> 99 <sup>a</sup>	11 200	10 600	6 000 <sup>b</sup>	1.17
3	8.0	> 99 <sup>a</sup>	2 400	2 500	3 500 <sup>c</sup>	1.38
3	0.5	> 99 <sup>a</sup>	5 100	5 300	4 700 <sup>c</sup>	1.42
4	1.0	> 99 <sup>a</sup>	14 600	14 500	9 700 <sup>c</sup>	1.21
4	0.5	98	5 000	4 900	5 500 <sup>c</sup>	1.30
5	2.0	> 99 <sup>a</sup>	18 700	—	31 500 <sup>c</sup>	1.86
5	0.5	98	6 000	—	15 000 <sup>c</sup>	1.89

<sup>a</sup> No residual monomer signal detected in <sup>1</sup>H NMR spectrum. <sup>b</sup> THF eluent; PMMA standards. <sup>c</sup> Aqueous eluent; PEO standards.



**Fig. 1** (a) Evolution of <sup>1</sup>H NMR spectra (D<sub>2</sub>O) for the homopolymerisation of OEGMA by ATRP at 20 °C in aqueous media using initiator 1. (b) Typical conversion vs. time curve derived from the <sup>1</sup>H NMR spectra: (◆) conversion and (■)  $\ln(M_0/M)$ .

As far as we are aware, there have been no previous reports of rapid ATRP in aqueous media at ambient temperature. However, ATRP of hydrophobic monomers at ambient temperature is well-documented. Haddleton *et al.* described<sup>8</sup> the relatively slow bulk polymerisation of methyl methacrylate at 25 °C, with 92% conversion requiring a reaction time of 20 h. In contrast, Matyjaszewski and co-workers reported<sup>9</sup> the rapid bulk polymerisation of methyl acrylate at 22 °C. In this latter case it was shown that the choice of ligand for the Cu<sup>I</sup> catalyst was critical for efficient polymerisation: much slower rates were obtained with a dialkyl-substituted bipyridine ligand than for a multifunctional ligand, hexamethylated tris[2-(dimethyl-amino)ethyl]amine. The same research group has also shown<sup>10</sup> that solvent polarity can be an important parameter in ATRP. Thus the rate of polymerisation of *n*-butyl acrylate in polar solvents such as ethylene carbonate was unexpectedly faster than that observed for bulk polymerisation, even though the monomer and initiator concentrations were significantly higher in the latter case. This observation was attributed to the

mononuclear nature of the Cu<sup>I</sup> catalyst. Since water is a very polar solvent, it is perhaps understandable that the ATRP of hydrophilic monomers such as OEGMA is particularly fast in aqueous media, even at room temperature. We also note that the Cu<sup>I</sup>[bpy]<sub>2</sub> catalyst is more likely to be mononuclear in aqueous media, with more complex binuclear halo-bridged structures being formed in non-aqueous media.<sup>11</sup> One referee believes that the rapid ATRP of OEGMA described herein is due to complexation of the ethylene oxide residues to the Cu catalyst. We believe that this hypothesis is unlikely because we observe similar rates of polymerization for the ATRP of unrelated monomers such as sodium 4-vinylbenzoate.<sup>12</sup> The second referee pointed out that, since OEGMA is a sterically hindered monomer, its rate coefficient for termination may be anomalously low; similar observations have been recently reported for *n*-dodecyl methacrylate.<sup>13</sup> This would be consistent with the apparent lack of termination observed even at high conversions (see Fig. 1). This referee also suggested that the Cu–Cl bond may be more easily cleaved in water than in non-aqueous media. Thus the rate of deactivation would be reduced and faster polymerisations would ensue.

In summary, ATRP of OEGMA is facile and well-controlled under environmentally-friendly conditions; this discovery has considerable potential for commercial exploitation.

We thank the EPSRC for financial support. We also thank the referees for their comments.

## Notes and references

- 1 J.-S. Wang and K. Matyjaszewski, *Macromolecules*, 1995, **28**, 7901; J.-S. Wang and K. Matyjaszewski, *J. Am. Chem. Soc.*, 1995, **117**, 5614; T. E. Patten and K. Matyjaszewski, *Adv. Mater.*, 1998, **10**, 901.
- 2 D. M. Haddleton, C. Waterson, P. J. Derrick, C. B. Jasieczek and A. J. Shooter, *Chem. Commun.*, 1997, 683.
- 3 S. Coca, C. B. Jasieczek, K. L. Beers and K. Matyjaszewski, *J. Polym. Sci., Polym. Chem. Ed.*, 1998, **36**, 1417.
- 4 X. Zhang, J. H. Xia and K. Matyjaszewski, *Macromolecules*, 1998, **31**, 5167; X. Zhang and K. Matyjaszewski, *Macromolecules*, 1999, **32**, 1763.
- 5 E. J. Ashford, V. Naldi, R. O'Dell, N. C. Billingham and S. P. Armes, *Chem. Commun.*, 1999, 1285.
- 6 K. Jankova, X. Y. Chen, J. Kops and W. Batsberg, *Macromolecules*, 1998, **31**, 538.
- 7 K. Matyjaszewski, K. L. Beers, A. Kern and S. G. Gaynor, *J. Polym. Sci., Polym. Chem. Ed.*, 1998, **36**, 823.
- 8 D. M. Haddleton, D. Kukulj, D. J. Duncalf, A. M. Heming and A. J. Shooter, *Macromolecules*, 1998, **31**, 5201.
- 9 J. H. Xia, S. G. Gaynor and K. Matyjaszewski, *Macromolecules*, 1998, **31**, 5958.
- 10 K. Matyjaszewski, Y. Nakagawa and C. B. Jasieczek, *Macromolecules*, 1998, **31**, 1535.
- 11 S. Kitagawa and M. Munakata, *Inorg. Chem.*, 1981, **20**, 2261.
- 12 X.-S. Wang, R. A. Jackson and S. P. Armes, submitted.
- 13 M. Buback and C. Kowolik, *Macromolecules*, 1999, **32**, 1445.

**This Page is Inserted by IFW Indexing and Scanning  
Operations and is not part of the Official Record**

**BEST AVAILABLE IMAGES**

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☒ **BLACK BORDERS**
- ☐ **IMAGE CUT OFF AT TOP, BOTTOM OR SIDES**
- ☐ **FADED TEXT OR DRAWING**
- ☐ **BLURRED OR ILLEGIBLE TEXT OR DRAWING**
- ☐ **SKEWED/SLANTED IMAGES**
- ☐ **COLOR OR BLACK AND WHITE PHOTOGRAPHS**
- ☐ **GRAY SCALE DOCUMENTS**
- ☒ **LINES OR MARKS ON ORIGINAL DOCUMENT**
- ☐ **REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY**
- ☐ **OTHER: \_\_\_\_\_**

**IMAGES ARE BEST AVAILABLE COPY.**

**As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.**

**THIS PAGE BLANK (USPTO)**